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- [54] Title: (-)-ISOPREGOL-CONTAINING PHYSIOLOGICAL COOLING AGENT AND COOLING COMPOSITION
- [57] Abstract: (Revised)

Goal: To propose a cooling agent and cooling composition characterized by the fact that it: 1) is not volatile, 2) has extremely low irritability, 3) has adequate cooling action, 4) does not crystallize in the base, 5) has low raw material cost, and 6) is readily soluble in a variety of bases.

Structure: Relates to a physiological cooling agent and physiological cooling composition containing (-)-isopregol, having the following structural formula (1):



and to cosmetics and medications for epidermal use or products suitable for oral use which contain said compound.

Effects: The (-)-isopregol of Structural Formula (1) has extremely little odor compared to L-menthol and when used in the mouth or on the skin, develops an adequate physiological cooling effect.

## Claims

1. Physiological cooling agent consisting of (-)-isopregol corresponding to Structural Formula (1):

### Formula 1



(1)

2. Physiological cooling composition containing the (-)-isopregol in accordance with Claim 1.

## Detailed Explanation of the Invention

### 0001

#### Field of Industrial Application

The invention relates to a physiological cooling agent and physiological cooling composition containing (-)-isopregol.

### 0002

#### Prior art

Known prior art chemical compounds with physiological cooling action on the skin and nasal mucosae, ie, the so-called cooling effect, were oil of mint and L-menthol, the chief constituent thereof, both of which were added as aromas to food materials, beverages, toothpastes and tobacco. Further, various cosmetic products and agents of topical application are widely used as cooling agents. However, although L-menthol has strong cooling action, it not only has the characteristic mint odor but also is subject to sublimation and can therefore hardly have a sufficiently long-lasting cooling action. Specifically, with regard to the characteristic mint odor, when [L-menthol] was added to various products such as cosmetics, one of the difficulties encountered was that the elegant scent of the cosmetic product was lost. Further, because of this sublimation, this drawback could not be adequately offset by use of dressings such as compresses, plasters and tape used specifically to prolong the cooling effect.

### 0003

Further, although the solid L-menthol is adequately mixed with and dissolved in the other medications and bases in the formulations intended for these dressings, it gradually crystallizes in the base after compounding, reducing the release of active principle and detracting from the cooling effect. In addition, other components must be added as solubilizers for the L-menthol because of these stability problems arising in the base. Further, L-menthol is a very expensive ingredient, making for onerous product costs.

0004

Recently, numerous patents have appeared concerning L-menthol derivatives and related compounds intended for odor attenuation. For example, Tokkai 1972-16647, Tokkai 1972-16649, Tokkai 1983-88334, Tokkai 1986-194049 and Tokkai 1990-290827 relate to menthol derivatives, while Tokkai 1983-93454, Tokkai 1983-95194 relate to tricyclic alcohols, and Tokkai 1985-136544 relates to tricyclic amides with cooling effects.

0005

#### Problems to be Solved by the Invention

Product formulations containing the aforementioned L-menthol and related products for use as cosmetics and medications are inadequate products because of drawbacks related to: 1) cooling effect, 2) durability of cooling effect, 3) peculiar odor (mint odor), 4) instability in the product, 5) cost effectiveness (product cost), 6) solubility, 7) sublimability.

0006

The sublimable product L-menthol's characteristic mint odor spreads over a wide area even in small quantities, irritating the eyes and nasal mucosae and creating unfavorable environmental conditions in manufacturing industries that process L-menthol. Further, problems were encountered in the use of products as well, because the mint odor tended to be offensive. Further, the sublimation tendency caused difficulties in maintaining the stability of products.

0007

Thus, the goal of the invention is to devise a cooling agent and cooling composition characterized by the fact that it: 1) does not sublime at ordinary temperatures, 2) develops less peculiar odor, 3) affords adequate cooling effect, 4) does not crystallize in the base, 5) is based on low-cost raw materials, and 6) has good solubility in various bases, when used to develop various products such as cosmetics for oral and topical use and medications for oral use.

0008

#### Means of Solving the Problem

The inventors conducted intensive research aimed at solving this problem, focusing primarily on (-)-isopregol (chemical name: (-)-2-isopropenyl-5-methylcyclohexanol), a compound related to L-menthol and corresponding to structural formula (1). When they tested for cooling effect, they discovered that it has a cooling effect similar to that of L-menthol, and this cooling effect is adequate even in applications in the mouth and on the skin.

0009

#### Formula 2



(1)

Further, they discovered that the compound has less characteristic odor than L-menthol and oil of mint and is non-volatile and highly stable.

0010

Further, because this compound is liquid at ordinary temperatures, there is no need to use additives such as solubilizers during processing, and its excellent mutual solubility with various bases affords a very desirable form for combining and mixing processes.

0011

Although (-)-isopregol exists in the essential oil of lemon grass and is widely used in blended oriental spices with rose and geranium flavor, and scents for soaps and other products or as a substance accompanying L-menthol, it has never been known to have a cooling effect. Nor have these materials ever been investigated with a view to finding constituents with a cooling effect.

0012

Indeed, there are no reports in the technical literature on any studies on these materials, let alone studies on cooling effects, and it was only through the intensive research of the inventors that the cooling effect of (-)-isopregol and cooling compositions made from it were discovered.

0013

(-)-Isopregol, discovered as a novel physiological cooling agent, can be contemplated for use in pharmaceuticals, nonpharmaceuticals or foods, and can be appropriately combined with the known bases or medications used in their formulation.

0014

Further, other constituents, such as preservatives, antioxidants, scents, pigments, and surfactants can be used as additives in these formulations provided the cooling effect of (-)-isopregol is not lost.

0015

Hence, the inventive physiological cooling agent can be used in a cooling composition to confer a cooling effect by adding it to pharmaceuticals such as ointments, creams, gels, lotions, aerosols, ready-made dressings and tapes; cosmetics such as powders, hair tonic, shampoo and lipstick; oral hygiene products such as toothpaste; and food products such as chewing gum, candy, frozen desserts and soft drinks.

0016

The amount of the cooling agent to be added is not particularly limited, but the amount used is preferably in the range of 0.01-5 wt% by weight.

0017

Known medications can appropriately be used as active principles in various products such as pharmaceuticals and cosmetics.

0018

**Embodiments**

The invention is described in detail on the basis of the following embodiments but is not limited thereto.

0019

**Embodiment 1. Lotion**

	(wt%)
ethanol	59.0
purified water	35.0
propylene glycol	5.0
(-)-isopregol	1.0

A cooling agent was prepared with the above formulation. Applied to the skin, it conferred a bracing menthol-like coolness.

0020

**Embodiment 2. Hair Tonic**

	(wt%)
ethanol	52.0
jojoba oil	0.4
polyoxyethylene sorbitan laurate	1.2
propylene glycol	1.2
trichlosan	0.1
pigment	trace
(-)-isopregol	0.5
purified water	balance

A hair tonic was prepared by uniformly mixing the above formulation. When this hair tonic was applied to the scalp, a refreshing cooling sensation remained after the cooling effect produced by evaporation of the ethanol.

0021

**Embodiment 3. Skin Lotion**

	(wt%)
ethanol	20.0
propylene glycol	5.0
glycerin	4.5
methyl paraoxybenzoate	0.1
fragrance	0.2
purified water	70.0
(-)-isopregol	0.2

A skin lotion was prepared by mixing the above-listed ingredients. When applied to the skin, it conferred a bracing cooling effect to the skin without irritation.

0022

**Embodiment 4. Toothpaste**

	(wt%)
calcium hydrogen phosphate	
carboxymethyl cellulose	50.0
sodium lauryl sulfate	1.0
glycerin	2.0
saccharin	25.0
fragrance	0.2
(-)-isopregol	0.8
purified water	0.05
	balance

A toothpaste was prepared by mixing the above-listed ingredients. When used, it conferred a refreshing cooling effect throughout the mouth.

0023

**Embodiment 5. Shampoo**

	(wt%)
sodium lauryl sulfate	12.0
purified water	87.5
(-)-isopregol	0.5

A shampoo was prepared by mixing and dispersing the above-listed ingredients. When this shampoo was used, it left a bracing cooling effect on the skin.

0024

**Embodiment 6. Cream**

	(wt%)
liquid paraffin	10.0
medium chain fatty acid triglycerides	5.0
polyethylene glycol monostearate	3.0
glycerin	5.0
carboxyvinyl polymer	1.0
diisopropylamine	0.4
methyl paraoxybenzoate	0.2
(-)-isopregol	2.0
purified water	balance

A cream was prepared by mixing the above-listed components. A refreshing effect was left at the place where it was applied to the skin.

0025

**Embodiment 7. Ointment**

	(wt%)
white vaseline	76.0
glycerin monostearate	10.0
tallow	10.0
silicone oil	1.0
(-)-isopregol	3.0

An ointment was prepared by mixing the above-listed ingredients. When applied to the skin, it conferred a menthol-like cooling effect.

0026

**Embodiment 8. Poultice**

	(wt%)
gelatin	5.0
sorbitol	10.0
carboxymethyl cellulose	3.5
glycerin	25.0
kaolin	7.0
sodium polyacrylate	3.0
(-)-isopregol	0.5
purified water	46.0

A poultice was prepared by mixing the above-listed components while heating to form a paste, which was then spread onto a cloth. The product had the same cooling effect as menthol.

0027

**Embodiment 9. Poultice**

	(wt%)
gelatin	6.0
polyvinyl alcohol	3.5
methoxyethylene-anhydrous maleic acid copolymer	2.5
glycerin	25.0
kaolin	5.0
sodium polyacrylate	2.0
(-)-isopregol	0.5
purified water	45.5



A poultice was prepared by mixing the above-listed components while heating to form a paste, which was then spread onto a cloth. The product had the same cooling effect as menthol.

0028

**Reference Example 1. Poultice**

	(wt%)
gelatin	5.0
sorbitol	10.0
carboxymethyl cellulose	3.5
glycerin	25.0
kaolin	7.0
sodium polyacrylate	3.0
L-menthol	0.5
crotamiton	1.0
purified water	45.0

A poultice was prepared by mixing the above-listed ingredients while heating to form a paste, which was spread on a cloth. Crotamiton was used as a solubilizer for the L-menthol in this example.

0029

**Reference Example 2. Poultice**

	(wt%)
gelatin	5.0
sorbitol	10.0
carboxymethyl cellulose	3.5
glycerin	25.0
kaolin	7.0
sodium polyacrylic acid	3.0
L-menthol	0.5
purified water	46.0

A poultice was prepared by mixing the above-listed ingredients while heating to form a paste, which was applied to a base cloth. This Reference Example 2 was prepared without the crotamiton used as a solubilizer for L-menthol in Reference Example 1.

**0030. Test Example 1**

The physiological cooling effect of (-)-isopregol in a 0.02% petroleum ether solution was tested by applying it to the tips of the tongues and to the forearms of 10 healthy adult males. As a standard, a 0.01% petroleum ether solution of L-menthol was used. The results are shown in Table 1. The cooling effect was rated on the following scale:

- +++ extremely strong cooling effect perceived
- ++ strong cooling effect perceived
- + cooling effect perceived
- cooling effect not perceived

0031

Table 1

Sample	Cooling Effects on the Tongue	Cooling Effects on the Inside Skin of the Forearm
(-)-isopregol	+++	++
L-menthol	+++	++

As clearly evidenced by the above results, (-)-isopregol had an adequate L-menthol-like cooling effect on both the tongue and skin.

## 0032. Test Example 2

The physiological cooling effects and scents of the poultices of Embodiment 8 and Reference Example 1 were tested by applying these to the dorsal region of the forearms of 26 healthy male subjects. The ratings were made by testing the items listed in the following. The results are shown in Table 2.

0033

The procedure used for evaluation was to have the subjects use the following scale to report the pertinent test results for the various test items.

0034

## Test Items and Scale of Test Results

- a) intensity of cooling
- |                |       |   |
|----------------|-------|---|
| strong cooling | _____ | 3 |
| little cooling | _____ | 2 |
| no cooling     | _____ | 1 |
- b) durability of cooling
- |                   |       |   |
|-------------------|-------|---|
| over 3 hours      | _____ | 3 |
| less than 3 hours | _____ | 2 |
| less than 1 hour  | _____ | 1 |
- c) speed of cooling
- |                 |       |   |
|-----------------|-------|---|
| within 5 min    | _____ | 3 |
| within 5-10 min | _____ | 2 |
| over 10 min     | _____ | 1 |
- d) intensity of odor
- |             |       |   |
|-------------|-------|---|
| strong odor | _____ | 3 |
| weak odor   | _____ | 2 |
| no odor     | _____ | 1 |

0035

The number of points assigned by the subjects' ratings for the 4 items listed above were totaled to obtain the averages for the 26 subjects in each item as shown in Table 2.

0036

Table 2

Sample	Intensity of Cool Sensation	Duration of Cool Sensation	Speed of Onset of Cool Sensation	Intensity of Odor
Embodiment 8 Poulitice	2.9	3.0	2.8	1.1
Reference Example 1 Poulitice	2.9	2.7	2.5	2.9

As shown by the above results, (-)-isopregol produces a cooling sensation equivalent to that of L-menthol and has a mild odor.

## 0037. Test Example 2

The poulitices of Embodiment 8 and Reference Example 2 were stored at 5°C and investigated for crystallization with elapsing time. The results are shown in Table 3.

0038

Table 3

Sample	Time Elapsed				
	start	1 day	3 days	7 days	14 days
Embodiment 8 Poulitice	○	○	○	○	○
Reference Example 2 Poulitice	○	○	×	×	×

○: no crystallization observed

×: crystallization observed

0039

As indicated by the above results, in Reference Example 2 without solubilizer added, the L-menthol crystallized with elapsing time, whereas (-)-isopregol remains dissolved in the base.

0040

## Effects of the Invention

The cooling agent consisting of (-)-isopregol and the cooling composition containing it have an adequate cooling action on both the mouth and skin, extremely little odor in comparison to L-menthol, and are easy to compound because the product is non-volatile and hence stable over time. Further, no solubilizer is needed because the compound is liquid at ordinary temperatures. Further, the product features the potential for development of a highly stable product without any industrial environmental

problems. Hence, the inventive cooling agent is an extremely useful product for application as a physiological cooling composition for conferring a cooling effect by addition to medicinal products such as ointments, creams, gels, lotions, aerosols, ready-made poultices, tapes and medications for internal use; cosmetic products such as powders, hair tonics, shampoos and lipsticks; oral hygiene products; and food products such as chewing gum, candy, frozen desserts and soft drinks.